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1.0 Scientific Abstract

Non-Hodgkin's lymphoma afflicts over 50,000 people per year. While many patients with intermediate or high grade lymphoma can be cured by conventional chemotherapy and radiotherapy, 60-50% of patients with intermediate grade NHL can expect to relapse or develop primary refractory disease. While conventional salvage chemotherapy is effective in producing a remission in 50 to 70% of cases, long-term remissions are seen in only 10% of cases. Recently, results from the PARMA trial have shown that high-dose chemotherapy (HDC) with peripheral blood progenitor cell transplantation (PBPCT) was effective in producing a higher response rate (84% vs 44%) and higher overall survival (53 vs 32% at 5 years) compared to standard dose therapy. This trial and others have now established that HDC with PBPCT is the standard of care for patients with relapsed or primary refractory disease. Despite these improved results, it has become clear that the benefit of HDC with PBPC transplant is inversely related to the patient's age-adjusted international prognostic index (IPI). While some in this group of high-risk patients will benefit from the HDC, most will go onto to relapse. New treatment strategies directed towards this poor risk group of patients is warranted.

One strategy that could complement the present standard of care for patients with high-risk relapsed or refractory NHL involves immediate post-transplant chemotherapy with an antimetabolite based treatment program. This strategy revolves around the observation that most, if not all patients who relapse post-transplant are known to have minimal residual disease. Often, no residual lymphoma can be detected in the immediate post-transplant period. This low volume disease state, based upon a number of mathematical and kinetic models of tumor growth, is thought to possess a high growth fraction, with most residual cells residing in a state of active DNA synthesis. These states of active cellular proliferation render cells sensitive to antimetabolites. However, because of the risk of graft failure and/or bone marrow aplasia post-transplant, most physicians are reluctant to administer chemotherapy, especially antimetabolites, during this period. A growing body of clinical evidence suggests there may be therapeutic merit in this approach. Strategies that could mitigate the vulnerability of a newly engrafted bone marrow may afford new and safer opportunities to deliver chemotherapy at an opportune time in the patient's management.

Myeloprotection, the concept of transferring drug resistance genes into hematopoietic progenitor cells, may represent one strategy for reducing graft susceptibility to chemotherapy. Recently, our laboratory has developed a novel fusion gene (F/S DHFR - CD) consisting of a double mutant dihydrofolate reductase (F/S DHFR) and cytidine deaminase (CD). This gene has been shown to confer high level resistance to antifolates and cytidine analogues in a number of somatic gene transfer experiments. In addition, experiments in a murine syngeneic tumor model demonstrated a therapeutic advantage for those animals treated with HDC, myeloprotection and post-transplant methotrexate. Those animals that received marrow protection (mutant DHFR) with post-transplant MTX had a significantly improved cure rate. In contrast, those animals that received no post-transplant treatment or mock gene transfer with post-transplant MTX died from progression of their disease or MTX toxicity.

This pilot protocol proposes to use an SFG vector from the Maloney murine leukemia virus (MMLV) to introduce a novel fusion gene (F/S-CD) into the CD34+ cells of high-risk patients undergoing PBPCT for NHL. Following engraftment, all patients will be treated with escalating doses of MTX and Ara-C, until a maximum tolerated dose is reached. All patients will be routinely monitored for signs of drug toxicity, and molecular evidence of gene expression in hematopoietic cells. In addition, while a secondary objective, the minimal disease status of each patient will be assessed and followed as a function of the therapy. The principle objectives of this study are to evaluate the degree of gene transfer and expression in hematopoietic cells following retroviral gene transfer in-patients undergoing a standard PBPC transplant.